Clinical And Molecular Studies of Holoprosencephaly Patients in Brazil.

Lucilene Arilho Ribeiro – Craniofacial Anomalies Rehabilitation Hospital, Molecular Genetic Laboratory, University of São Paulo, Bauru, SP, Brazil. Tel: 55 (14) 31030916, fax: 55 (14) 2305191
e-mail: genetmol@adaptanet.com.br

Holoprosencephaly (HPE) is a common, severe malformation of the brain that involves separation of the central nervous system into left and right halves. Mild HPE can consist of signs such as a single central incisor, hypotelorism, microcephaly, or other craniofacial findings that can be presented with or without associated brain malformations (1,2). HPE aetilogically heterogeneous and exhibits wide phenotypic variation (3). In the past few years, positional cloning efforts have succeeded in discovering several genes in which mutations result in HPE. These includes *SHH* (4), *ZIC2* (5), *SIX3* (6), and *TGIF* (7).

Here we present an overview of the study that has been developed at Craniofacial Anomalies Rehabilitation Hospital – USP/Bauru, Brazil. We have reported 114 HPE patients at our hospital. These patients were divided into 4 groups aiming to facilitate the present study.

Group 1. Autosomal dominant inheritance HPE patients.
The patients in group 1 are phenotypically varied showing from slight to severe characteristics of the disease. The cytogenetic analysis showed a normal karyotype in all cases. Either the father or the mother has a single central incisor, thus demonstrating that they are carriers. The *SHH* and *ZIC2* genes analysis has been performed. We have a total of 23 patients in this group.

Group 2. HPE patients and anophthalmia.
The patients in group 2 show classical holoprosencephaly phenotype, ocular involvement and normal karyotype. All cases of the present sample are isolated. The whole clinical picture of our patients clearly excludes most of the known syndromes with holoprosencephaly, except the Zwetsloot syndrome, that shares several signs. The hypothesis of an autosomal recessive condition could be considered, taking into account the previosly reported patients (Zwetsloot et al., 1988). We are working on *SHH* and *SIX3* genes in these patients. The number of patients in this group is 9.

Group 3. HPE patients with normal development.
The patients in group 3 show lobar HPE phenotype characterisitcs, nevertheless they show normal neurologic development. The CT scan was normal for all patients, just the same we do not have MRI for this patients. Cytogenetic analysis revealed normal karyotype fo all patients. Most of the patients in this group work and/or study having an excellent performance. *SHH*, *ZIC2* and *SIX3* genes analysis has been performed. There are 24 patients included in this group.

Group 4. HPE patients.
This group is made of the remaining patients who show classical phenotype of HPE ranging from slight to severe. The mode of inheritance is unknown. We are performing cytogenetic and molecular analysis in this group. There is a total of 58 patients in this group.

References

1. Cohen, M.M. Perspectives on holoprosencephaly. Part I. Epidemiology, genetics, and syndromology. Teratology 40, 221-235 (1989).
2. Cohen, M.M. Perspectives on holoprosencephaly. Part II. Spectra, distinctions, continuities, and discontinuities. Am. J. Med. Genet. 34, 371-388 (1989).
3. Roessler, E.; Muenke, M. Review. Holoprosencephaly: a paradigm for the complex genetics of brain development. J. Inherit. Metab. Dis. 21, 481-497 (1998).
4. Nanni, L., Ming, J.E., Bocian, M., Steinhaus, K, Bianchi, D.W., DieSmulders, C., Giannoti, A, Imaizumi, K., Jones, K.L., Campo, M.D. The mutational spectrum of the sonic hedgehog gene in

holoprosencephaly: SHH mutations cause a significant proportion of autosomal dominant holoprosencephaly. Hum. Mol. Genet. 8, 2479-2488 (1999).

5. Brown, S.A, Warburton, D., Brown, L.Y., Yu, C.Y., Roeder, E.R., Stengel-Rutkowski, S., Hennekan, R.C., Muenke, M. Holoprosencephaly due to mutations in ZIC2,a homologue of *Drosophila odd-paired*. Nature Genet. 20, 180-183 (1998).
6. Wallis, D.E., Roessler, E., Hehr, U., Nanni, L., Wiltshire, T., Richieri-Costa, A, Gillessen-Kaesbach, G., Zackai, E.H., Rommens, J. Muenke, M. Mutations in the homeodomain of the human SIX3 gene cause holoprosencephaly. Nature Genet. 22-196-198 (1999).
7. Gripp, K.W., Wotton, D., Edwards, M.C., Roessler, E., Ades, L., Meinecke, P., Richieri-Costa, A, Zackai, E.H., Massahue, J., Muenke, M. Mutations in TGIF cause holoprosencephaly and link nodal signalling to human neural axis determination. Nature Genet. 25, 205-208 (2000).